COMPOSITIONS AND METHODS FOR COMBINATION ANTIVIRAL THERAPY

This non-provisional application is a continuation of U.S. patent application Ser. No. 10/540,794, filed Mar. 20, 2006, which is a national stage entry of PCT/US04/00832, filed Jan. 13, 2004 which claims the benefit of Provisional Application Nos. 60/440,246 and 60/440,308, both filed Jan. 14, 2003, which is incorporated herein by reference.

FIELD OF THE INVENTION

The invention relates generally to combinations of compounds with antiviral activity and more specifically with anti-HIV properties. In particular, it relates to chemically stable combinations of structurally diverse anti-viral agents.

BACKGROUND OF THE INVENTION

Human immunodeficiency virus (HIV) infection and related diseases are a major public health problem worldwide. Human immunodeficiency virus type 1 (HIV-1) encodes at least three enzymes which are required for viral replication: reverse transcriptase (RT), protease (Prt), and integrase (Int). Although drugs targeting reverse transcriptase and protease are in wide use and have shown effectiveness, particularly when employed in combination, toxicity and development of resistant strains have limited their usefulness (Palella, et al *N. Engl. J. Med.* (1998) 338:853-860; Richman, D. D. *Nature* (2001) 410:995-1001). Human immunodeficiency virus type 1 (HIV-1) protease (Prt) is essential for viral replication and is an effective target for approved antiviral drugs. The HIV Prt cleaves the viral Gag and Gag-Pol polyproteins to produce viral structural proteins (p17, p24, p7 and p6) and the three viral enzymes. Combination therapy with RT inhibitors has proven to be highly effective in suppressing viral replication to unquantifiable levels for a sustained period of time. Also, combination therapy with RT and Prt inhibitors (PI) have shown synergistic effects in suppressing HIV replication. Unfortunately, a high percentage, typically 30 to 50% of patients currently fail combination therapy due to the development of drug resistance, non-compliance with complicated dosing regimens, pharmacokinetic interactions, toxicity, and lack of potency. Therefore, there is a need for new HIV-1 inhibitors that are active against mutant HIV strains, have distinct resistance profiles, fewer side effects, less complicated dosing schedules, and are orally active. In particular, there is a need for a less onerous dosage regimen, such as once per day oral dosing, optimally with as few pills as possible.

The use of combinations of compounds can yield an equivalent antiviral effect with reduced toxicity, or an increase in drag efficacy. Lower overall drug doses can reduce the frequency of occurrence of drug-resistant variants of HIV. Many different methods have been used to examine the effects of combinations of compounds acting together in different assay systems (Furman WO 02/068058). Lower doses predict better patient compliance when pill burden decreases, dosing schedules are simplified and, optionally, if synergy between compounds occurs (Loveday, C. "Nucleoside reverse transcriptase inhibitor resistance" (2001) *JAIDS Journal of Acquired Immune Deficiency Syndromes* 26:S10-S24). AZT (Zidovudine™, 3'-azido, 3'-deoxythymidine) demonstrates synergistic antiviral activity in vitro in combination with agents that act at HIV-1 replicative steps other than reverse transcription, including recombinant soluble CD4 castanospermine and recombinant interferon-α. However, it must be noted that combinations of compounds can give rise to increased cytotoxicity. For example, AZT and recombinant interferon-α have an increased cytotoxic effect on normal human bone marrow progenitor cells.

Chemical stability of combinations of antiviral agents is an important aspect of co-formulation success and the present invention provides examples of such combinations.

There is a need for new combinations of orally-active drugs for the treatment of patients infected with certain viruses, e.g. HIV, that provide enhanced therapeutic safety and efficacy, impart lower resistance, and predict higher patient compliance.

SUMMARY OF THE INVENTION

The present invention provides combinations of antiviral compounds, in particular compositions and methods for inhibition of HIV. In an exemplary aspect, the invention includes a composition including tenofovir disoproxil fumarate and emtricitabine which has anti-HIV activity. The composition of tenofovir DF and emtricitabine is both chemically stable and either synergistic and/or reduces the side effects of one or both of tenofovir DF and emtricitabine. Increased patient compliance is likely in view of the lower pill burden and simplified dosing schedule.

The present invention relates to therapeutic combinations of [2-(6-amino-purin-9-yl)-1-methyl-ethoxymethyl]-phosphonic acid diisopropoxycarbonyloxymethyl ester fumarate (tenofovir disoproxil fumarate, tenofovir DF, TDF, Viread®) and (2R, 5S, cis)-4-amino-5-fluoro-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one (emtricitabine, Emtriva™, (-)-cis FTC) and their use in the treatment of HIV infections including infections with HIV mutants bearing resistance to nucleoside and/or non-nucleoside inhibitors. The present invention is also concerned with pharmaceutical compositions and formulations of said combinations of tenofovir disoproxil fumarate and emtricitabine. Another aspect of the invention is a pharmaceutical formulation comprising a physiologically functional derivative of tenofovir disoproxil fumarate or a physiologically functional derivative of emtricitabine.

Therapeutic combinations and pharmaceutical compositions and formulations of the invention include the combination of PMEA or PMPA (tenofovir) compounds with emtricitabine or (2R, 5S, cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one (3TC, lamivudine, Epivir™), and their use in the treatment of HIV infections.

One aspect of the invention is a method for the treatment or prevention of the symptoms or effects of an HIV infection in an infected animal which comprises administering to, i.e. treating, said animal with a therapeutically effective amount of a combination comprising [2-(6-ammo-purin-9-yl)-1-methyl-ethoxymethyl]-phosphonic acid diisopropoxycarbonyloxymethyl ester fumarate (tenofovir DF, TDF) or a physiologically functional derivative thereof, and (2R, 5S, cis)-4-amino-5-fluoro-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one (emtricitabine) or a physiologically functional derivative thereof.

Another aspect of the invention is a unit dosage form of a therapeutic combination comprising tenofovir disoproxil fumarate and emtricitabine, or physiological functional derivatives thereof. The unit dosage form may be formulated for administration by oral or other routes and is unexpectedly chemically stable in view of the properties of the structurally diverse components.

Another aspect of the invention is directed to chemically stable combination antiviral compositions comprising tenofovir disoproxil fumarate and emtricitabine. In a further